

EXHIBIT E



MMWR™

Morbidity and Mortality Weekly Report



Weekly

December 13, 2002 / Vol. 51 / No. 49

***Exophiala* Infection from Contaminated Injectable Steroids Prepared by a Compounding Pharmacy — United States, July–November 2002**

In the United States, pharmacists compound medications to meet unique patient drug requirements or to prepare drug products that are not available commercially (1). In September 2002, the North Carolina Division of Public Health (NCDPH) was notified of two cases of meningitis caused by a rare fungus in patients who had received epidural injections at outpatient pain management clinics. This report describes five cases of fungal infection associated with contaminated drugs prepared at a compounding pharmacy. Clinicians should consider the possibility of improperly compounded medications as a source of infection in patients after epidural or intra-articular injections.

Case Reports

Case 1. On July 5, 2002, a woman aged 77 years with chronic low back pain was admitted to hospital A in North Carolina with a 4-day history of progressive diffuse headache, fever, chills, and malaise with subsequent development of vertigo, nausea, and vomiting. She was febrile (100.4° F [38.0°C]) and had slight nuchal rigidity. Analysis of cerebrospinal fluid (CSF) was consistent with meningitis: 979 white blood cells (WBC)/mm³ (normal: <10 WBC/mm³) with 63% neutrophils, protein of 134 mg/dL (normal: 15–45 mg/dL), and glucose of 38 mg/dL (normal: 40–80 mg/dL). The patient showed no improvement on antibacterial drugs, and a follow-up CSF analysis on July 18 revealed yeast-like elements on microscopic examination. The patient was treated with amphotericin B and transferred to hospital B in North Carolina. On July 24, a fungus cultured from CSF was identified as *Exophiala* (*Wangiella*) *dermatitidis*. Amphotericin B was discontinued, and voriconazole and flucytosine were started. The patient's condition continued to deteriorate, and she died 51 days after hospitalization. The patient had been treated at pain

management clinic A in North Carolina and had received lumbar epidural injections with methylprednisolone acetate 100 and 35 days before hospital admission. The injectable methylprednisolone had been prepared by compounding pharmacy A in South Carolina.

Case 2. On August 14, 2002, a woman aged 61 years who was being treated for chronic low back pain at pain management clinic A was admitted to hospital A after CSF obtained during a myelogram was consistent with meningitis (820 WBC/mm³ with 52% neutrophils, protein of 108 mg/dL, and glucose of 57 mg/dL). The patient had a 3–5 day history of mild headache, subjective fever, chills, sweats, and mild neck stiffness. The patient had received lumbar epidural injections at pain management clinic A 84 and 34 days before hospital admission. The injections contained methylprednisolone acetate prepared by compounding pharmacy A. CSF grew yeast, later identified as *E. dermatitidis*, 27 days after collection. The patient was begun on intravenous voriconazole and later switched to oral voriconazole; as of December 5 (70 days into therapy), she has improved.

Additional cases. Clinicians from hospital A notified NCDPH of the two cases of *E. dermatitidis* meningitis; three additional cases have been identified. Case 3 occurred in a woman aged 71 years who had *E. dermatitidis* meningitis. She was admitted to hospital B in North Carolina on July 8 and had received epidural methylprednisolone acetate injections at pain management clinic B 82, 55, and 35 days before

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PSC-EX_0014

The *MMWR* series of publications is published by the Epidemiology Program Office, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

SUGGESTED CITATION

Centers for Disease Control and Prevention. [Article title]. *MMWR* 2002;251[Quintile page numbers].

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hospitalization. Case 4 occurred in a woman aged 65 years who had *E. dermatitidis* meningitis. She was admitted to hospital C in North Carolina on October 8 and had received epidural methylprednisolone acetate injections at pain management clinic A 116 days before hospitalization. Case 5 occurred in a woman aged 52 years who had *E. dermatitidis* sacroiliitis. She was admitted to hospital D in North Carolina on November 4 and had received intra-articular methylprednisolone acetate injections at pain management clinic B 103 and 152 days before hospitalization.

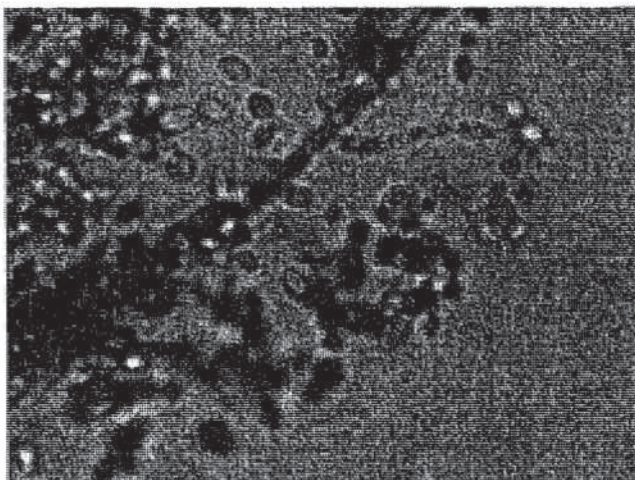
Investigation of Compounding Pharmacy A

Compounding pharmacy A was the source of the methylprednisolone acetate administered to all five patients with *Exophiala* infections. The pharmacy had been supplying the compounded product to hospitals and pain management clinics in five states after a proprietary form of methylprednisolone acetate injectable suspension (Depo Medrol®, Pharmacia Corp., Peapack, New Jersey) became difficult to obtain from the manufacturer. An investigation of compounding pharmacy A by the South Carolina Board of Pharmacy (SCBP) found improper performance of an autoclave with no written procedures for autoclave operation, no testing for sterility or appropriate checking of quality indicators, and inadequate clean-room practices as outlined in the American Society of Health-System Pharmacists (ASHP) guidance for pharmacy-prepared sterile products (2). Microbiologic culture at CDC and the Food and Drug Administration (FDA) of unopened vials from three separate lots of injectable methylprednisolone obtained from compounding pharmacy A yielded *E. dermatitidis* (Figure). On September 27, SCBP ordered the pharmacy to halt further sale of compounded drug products. Injectable drugs had been distributed to physicians, hospitals, clinics, and consumers in 11 states (Connecticut, Illinois, Indiana, Kentucky, Louisiana, Massachusetts, Mississippi, New Hampshire, North Carolina, South Carolina, and Virginia). FDA inspection of the compounding facility revealed that the firm failed to have adequate controls to ensure necessary sterility, including the absence of appropriate testing for potency and sterility before distribution. On November 15, based on the lack of assurance that the pharmacy's products were sterile, FDA announced a nationwide alert about all injectable drug products prepared by the pharmacy.

All sites that received injectable methylprednisolone prepared by compounding pharmacy A have been contacted and have returned all unused products for testing. Treating clinicians were informed of the investigation of the adulterated product. In two states, patients who might have received the product were sent letters directing them to seek medical

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FIGURE. Slide culture of *Exophiala (Wangliella) dermatitidis* stained with lactophenol blue demonstrating conidial structure and numerous budding cells, magnified by 1,000



attention if they developed symptoms, and laboratories were instructed to notify state officials if they isolated *E. dermatitidis* from clinical specimens.

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Editorial Note: As of December 5, five cases of *Exophiala* infection associated with injectable medication from compounding pharmacy A had occurred. Cases occurred up to 152 days following an injection.

Pharmacy compounding is the process of combining drug ingredients to prepare medications that are not commercially available or to alter commercially available medications to meet specific patient needs such as dye-free or liquid formulations (3). The practice of compounding has been reported to be increasing with an estimated 43,000 compounded medications prepared daily in the United States (4,5). Pharmacists traditionally have prepared medications to fulfill individual prescription requests or manipulated reasonable quantities of

human drugs on receipt of a valid prescription for an individually identified patient from a licensed practitioner. Some compounding is legal under state laws, and, when appropriate, FDA can exercise its enforcement discretion regarding new drugs and certain other requirements of the federal Food, Drug, and Cosmetic Act (6).

On-site investigation of compounding pharmacy A by state and federal regulators identified several instances of nonadherence to sterile technique. Microbiologic cultures at CDC and FDA of methylprednisolone from unopened vials prepared by compounding pharmacy A yielded isolates of *E. dermatitidis*. This fungus caused the death from meningitis in one patient, sacroiliitis in another, and meningitis in three other patients who had received either epidural or intra-articular injections of methylprednisolone compounded at pharmacy A. Other recent clusters of infections associated with products prepared by compounding pharmacies include *Serratia* meningitis from epidural injections of betamethasone in California (Contra Costa Health Services, unpublished data, 2002) and *Chryseomonas* meningitis from epidural injections of methylprednisolone in Michigan (CDC, unpublished data, 2002). These meningitis clusters all occurred among patients who received epidural injections for chronic pain management.

E. dermatitidis is a neurotropic, dark pigment-forming fungus found in soil and is an uncommon cause of human illness (7). Limited data are available on treatment; however, in vitro data suggest that amphotericin B, itraconazole, terbinafine, and voriconazole might be effective (8). Isolates from four of the five infected persons reported were tested in vitro and were susceptible to voriconazole, itraconazole, and amphotericin B. Voriconazole was chosen for treating the five persons reported because of in vitro susceptibility results and availability of an oral form of the drug.

Clinicians or laboratorians diagnosing any cases of *Exophiala* should determine if the patient had received injections of methylprednisolone in the last year. Although the implicated product has been recalled, clinicians should be aware that cases might still occur because of the possible long incubation period of the fungal infection. Patients with possible injection-associated *Exophiala* infections should be reported to their state health department and to CDC, telephone 800-893-0485; such information should be exchanged rapidly with other state and local health departments. Clinicians should consider the possibility of contaminated medication as a source of infection in patients after epidural or intra-articular injections. Compounding pharmacies should ensure that pharmacy staff are trained appropriately and that proper sterile technique is followed in accordance with existing standards from ASHP (2) and the United States Pharmacopeia (<http://www.usp.org>). FDA has outlined specific activities that

help distinguish the role of compounding pharmacies from pharmaceutical manufacturing (4).

Some health-system pharmacists might not realize that they are purchasing injectables prepared through compounding (1). Purchasers of pharmaceuticals should determine if supplies are provided from a compounding pharmacy that is licensed in their state and that follows appropriate measures to ensure that injectable products are free of contamination. In most states, compounding pharmacies are not required to report adverse events associated with their products to state or federal agencies. Such reporting to FDA is required for pharmaceutical manufacturing companies. Health-care professionals and compounding pharmacies are urged to report contaminated compounded drug products or adverse events associated with compounded drug products to their state boards of pharmacy and health departments. To help prevent further cases, practitioners also are encouraged to submit such reports to FDA's MedWatch program by telephone at 1-800-332-1088 or at <http://www.fda.gov/medwatch/report.htm>.

References

1. Young D. Outsourced compounding can be problematic: community pharmacies linked to contaminated injectables. Available at http://www.ashp.org/public/pubs/ajhp/current/12a-news_outsourced.pdf.
2. American Society of Health-System Pharmacists. ASHP guidelines on quality assurance for pharmacy-prepared sterile products. *Am J Health Sys Pharm* 2000; 57:1150-69.
3. International Academy of Compounding Pharmacists. About compounding. Available at http://www.iacprx.org/about_compounding/index.html.
4. Smith LK. Regulatory and operational issues of founding a compounding pharmacy. *International Journal of Pharmaceutical Compounding* 2002;6:434-7.
5. Professional Compounding Centers of America. History of compounding. Available at http://www.pccarx.com/about_comp.asp.
6. U.S. Food and Drug Administration. Compliance policy guidance for Food and Drug Administration staff and industry. Section 460-200, pharmacy compounding. Available at http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html.
7. Matsumoto T, Matsuda T, McGinnis MR, Ajello L. Clinical and mycological spectra of *Wangiella dermatitidis* infections. *Mycoses* 1993;36:145-55.
8. Meletiadis J, Meis JF, de Hoog GS, Verweij PE. *In vitro* susceptibilities of 11 clinical isolates of *Exophiala* species to six antifungal drugs. *Mycoses* 2000;43:309-12.

Outbreaks of Gastroenteritis Associated with Noroviruses on Cruise Ships — United States, 2002

During January 1–December 2, 2002, CDC's Vessel Sanitation Program (VSP), which conducts surveillance for acute gastroenteritis (AGE) on cruise ships with foreign itineraries sailing into U.S. ports (1), received reports of 21 outbreaks of

AGE* on 17 cruise ships. Of the 21 outbreaks, nine were confirmed by laboratory analysis of stool specimens from affected persons to be associated with noroviruses, three were attributable to bacterial agents, and nine were of unknown etiology. Seven outbreaks were reported in 2001, and of these, four were confirmed to be associated with norovirus (CDC, unpublished data, 2002). This report describes five of the norovirus outbreaks that occurred during July 1–December 2, 2002, on cruise ships.

Outbreaks

Cruise Ship A. On July 18, cruise ship A, owned by cruise line A, embarked 1,318 passengers and 564 crew members for a 7-day cruise from Vancouver to Alaska. On July 19, five passengers reported to the ship's infirmary with symptoms of AGE (Figure 1). By July 25, a total of 167 (13%) passengers and nine (2%) crew members had reported illness. Among the 176 patients, the predominant symptoms were vomiting (76%) and diarrhea (73%). Five of 10 stool specimens from ill passengers were positive for norovirus by reverse transcriptase polymerase chain reaction (RT-PCR). On July 25, when passengers disembarked, the ship was disinfected in accordance with CDC recommendations, and the same day, a new group of passengers embarked for another 7-day cruise. During the cruise, 189 (14%) of 1,336 passengers and 30 (5.3%) of 571 crew members had AGE with diarrhea (91%) and vomiting (85%) (Figure 1). An environmental health inspection conducted by CDC revealed no sanitary deficiencies. Cruise line A cancelled a subsequent cruise and voluntarily took the ship out of service for 1 week for aggressive cleaning and sanitizing. No outbreaks were reported on subsequent cruises.

Cruise Ship B. On October 1, cruise ship B, also owned by cruise line A, embarked 1,281 passengers and 598 crew members for a 21-day cruise from Washington to Florida. By October 16, a total of 101 (8%) passengers and 14 (2%) crew members reported to the infirmary with AGE symptoms. On October 18, CDC investigators boarded the ship to conduct an epidemiologic and environmental investigation. Of 972 surveyed passengers, 399 (41%) met the case definition for AGE. Investigators found no association between illness and water, specific meals served on the ship, or with offshore excursions. Stool specimens from 12 of 13 patients tested posi-

*An outbreak of AGE was defined as one in which $\geq 3\%$ of passengers or crew members report illness (defined as three or more episodes of loose stools in a 24-hour period or as vomiting with one additional symptom such as abdominal cramps, headache, myalgia, or fever). The evaluation of an outbreak might consist of environmental, epidemiologic, and laboratory investigative components, including an epidemic survey distributed to passengers and crew members, environmental sampling, and collection of stool specimens from patients.